Treatment of Vancomycin-Resistant *Enterococcus* with Quinupristin/Dalfopristin and High-Dose Ampicillin

J Audis Bethea, Christine M Walko, and Patricia A Targos

**OBJECTIVE:** To report the successful treatment of vancomycin-resistant *Enterococcus* (VRE) bacteremia using the combination of quinupristin/dalfopristin and high-dose ampicillin.

**CASE SUMMARY:** A 38-year-old African American woman with relapsed acute myeloid leukemia and neutropenic fever developed VRE bacteremia following 3 successive courses of vancomycin for methicillin-resistant staphylococcal infections. Treatment with linezolid was initiated; however, after 9 days of therapy, blood cultures continued to reveal VRE and the patient became febrile. The patient was subsequently switched to quinupristin/dalfopristin and high-dose ampicillin. The fever resolved and all subsequent blood cultures were negative after the initiation of combination therapy.

**DISCUSSION:** The emergence of VRE infections presents a treatment challenge in immunocompromised patients. When treating VRE infections in this patient population, the effectiveness of linezolid and quinupristin/dalfopristin is limited by their bacteriostatic activity when used as monotherapy. Recent in vitro data suggest synergistic activity with quinupristin/dalfopristin when used in combination with other antimicrobials in selected isolates of VRE.

**CONCLUSIONS:** Persistent VRE bacteremia was successfully treated in this neutropenic patient using the combination of high-dose ampicillin and quinupristin/dalfopristin. Case reports and in vitro data suggest that concomitant therapy with high-dose ampicillin may be an effective treatment alternative for VRE infections not responding to standard therapy.

**KEY WORDS:** ampicillin, linezolid, neutropenic fever, quinupristin/dalfopristin, vancomycin-resistant enterococcus.


Case Report

A 38-year-old African American female patient with relapsed acute myeloid leukemia developed neutropenic fever and stage III bone marrow necrosis (white blood cell count <0.1 x 10^9/mm^3) following combination chemotherapy with a fludarabine, cytarabine, and filgrastim (FLAG) regimen.13 Broad-spectrum intravenous antimicrobial therapy with tobramycin 300 mg daily and cefazidime 2 g every 8 hours was empirically initiated for neutropenic fever. Initial blood cultures obtained during FLAG therapy yielded methicillin-resistant Staphylococcus epidermidis (MRSE), resulting in the addition of a 10-day course of vancomycin therapy. Additional blood cultures were negative; however, conventional amphotericin B therapy was added due to persistent fevers. The patient subsequently received 2 additional treatment courses of vancomycin secondary to MRSE bacteremia and a methicillin-resistant Staphylococcus aureus urinary tract infection.

Thirty-five days after the development of neutropenic fever and 6 days following the initiation of the third course of vancomycin therapy, blood cultures revealed vancomycin-resistant E. faecium. Susceptibility testing was remarkable for high-level resistance to streptomycin (minimum inhibitory concentration [MIC] >2000 µg/mL) and gentamicin (MIC >500 µg/mL), as well as resistance to ampicillin (MIC ≥16 µg/mL) and vancomycin (MIC ≥2 µg/mL). Antimicrobial activity was noted with linezolid (MIC ≤2 µg/mL) and quinupristin/dalfopristin (MIC ≤1 µg/mL). Based on these results, vancomycin was discontinued, intravenous linezolid 600 mg every 12 hours was initiated, and all intravascular devices were replaced. Despite continued isolation of VRE throughout the course of linezolid therapy, the patient remained afebrile and clinically stable until day 9. During this period, subsequent VRE isolates retained identical susceptibility profiles to that of the original isolate.

Due to persistent bacteremia and a recurrence of fever on day 9 of linezolid therapy, a transesophageal echocardiogram (TTE) was obtained, and all intravascular access devices were once again replaced. The TTE failed to note valvular vegetations consistent with endocarditis; however, due to the recurrence of fever and persistent bacteremia, linezolid was replaced with intravenous quinupristin/dalfopristin 7.5 mg/kg every 8 hours and ampicillin 4 g every 4 hours. Fever resolved and blood cultures were negative 2 days following the initiation of combination therapy. The patient continued to receive empiric antimicrobial therapy for gram-negative and fungal organisms during concomitant therapy with quinupristin/dalfopristin and high-dose ampicillin for 21 days.

Clinical markers of renal and hepatic function remained normal throughout the treatment course, and the patient’s only complication of therapy involved myalgias, which is a well-documented adverse effect of quinupristin/dalfopristin.11,12 Antibiotic therapy for the patient’s VRE bacteremia was successful, as demonstrated by resolution of clinical symptoms related to infection and clearance of the organism from blood cultures. Despite these efforts, the patient died due to multiple organ failure one month following resolution of the infection.

Discussion

In vitro data demonstrate synergistic activity with quinupristin/dalfopristin when used in combination with other antimicrobials in selected isolates of VRE.14,15 One study examined the antimicrobial activity of quinupristin/dalfopristin at concentrations of 2 µg/mL in combination with various antimicrobials on 50 clinical isolates of E. faecium.14 Synergy was exhibited in 3 strains with the addition of ampicillin (64 µg/mL) and in 4 strains following the addition of doxycycline (4–8 µg/mL). Another study reported checkerboard susceptibility data, demonstrating synergistic activity of ampicillin/sublactam, doxycycline, and vancomycin when used with quinupristin/dalfopristin at concentrations of 0.06–8.0 µg/mL.15 Synergistic activity was present with ampicillin/sublactam (0.25–128 µg/mL) in 3 strains, doxycycline (0.125–16 µg/mL) in 6 strains, and vancomycin (0.25–32 µg/mL) in 2 strains.

Case reports have also demonstrated the efficacy of combination antimicrobial therapy for VRE infections.16-18 A 53-year-old hemodialysis patient developed an intra-abdominal infection and bacteremia due to VRE.16 After the infection failed to resolve with chloramphenicol, doxycycline, and ciprofloxacin, the patient was successfully treated with intravenous ampicillin 2 g every 6 hours and streptomycin 500 mg twice weekly. VRE bacteremia was eradicated in a 65-year-old liver transplant patient with high-dose (30 g/day) continuous infusion of ampicillin/sublactam (serum ampicillin concentration 130 µg/mL) and gentamicin 50 mg every 12 hours.17

Combination therapy with high-dose ampicillin has demonstrated in vitro and clinical efficacy in the eradication of VRE. The incidence of synergistic activity varies and, in some cases, has been inconsistent. These inconsistencies are illustrated by the varied MICs at which in vitro (≤256 µg/mL) and in vivo (≤64 µg/mL) synergism has been documented.14,17 Although an MIC was not obtained for ampicillin in our patient’s isolate, an E-test analysis of the MIC may be useful when considering combination therapy. Furthermore, an evaluation of ampicillin’s synergistic activity may be indicated in strains of VRE possessing high-level ampicillin resistance (MIC ≥64 µg/mL). This should not, however, preclude the institution of combination therapy with high-dose ampicillin following clinical failure of traditional therapy.

Additional consideration must be given to the use of ampicillin/sublactam for VRE infections failing to respond to initial therapy. In vitro data indicate that select VRE strains have lower MICs for ampicillin/sublactam compared with ampicillin.15,17 These findings have been supported by a report of successful treatment of VRE infection with ampicillin/sublactam following clinical failure with high-dose ampicillin.17 Although the VRE bacteremia in our patient may have responded to quinupristin/dalfopristin, ampicillin/sublactam, or high-dose ampicillin alone, combination therapy was implemented due to treatment failure using a bacteriostatic agent as monotherapy. In this neutropenic patient, persistent VRE bacteremia was successfully treated using the combination of high-dose ampicillin and quinupristin/dalfopristin.

Summary

The treatment of VRE infections in immunocompromised patients is limited by the bacteriostatic activity of the available antimicrobial agents. In our neutropenic patient, persistent VRE bacteremia was successfully treated using the combination of high-dose ampicillin and quinupristin/dalfopristin. Case reports and in vitro data suggest that concomitant therapy with high-dose ampicillin may be an effective treatment alternative for VRE infections not responding to standard therapy.

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References


CONCLUSIONS: Una bacteremia persistente causada por VRE en un paciente neutropénico fue tratada exitosamente con ampicilina en dosis altas junto con quinupristin/dalfopristin. Datos in vitro y reportes de casos sugieren que esta combinación puede ser una alternativa de tratamiento efectiva para infecciones por VRE que no responden a tratamiento estándar.

Wanda T Maldonado

ÉXTRACTO

OBJETIVO: Informar el uso exitoso de quinupristin/dalfopristin en combinación con dosis altas de ampicilina en el tratamiento de una bacteremia causada por Enterococcus resistente a vancomicina (VRE).

RESUMEN: Se informa el tratamiento exitoso de una bacteremia por Enterococcus resistente a vancomicina con el uso concomitante de quinupristin/dalfopristin y dosis altas de ampicilina, luego de que fracasara el tratamiento con linezolid en un paciente neutropénico de 38 años de edad.

DISCUSIÓN: El surgimiento de infecciones causadas por VRE representa un reto en pacientes inmunocomprometidos. Cuando se tratan las infecciones causadas por VRE en estos pacientes, la efectividad de linezolid y quinupristin/dalfopristin se ve limitada por su efecto bacteriostático cuando se utilizan como monoterapia. Datos recientes obtenidos in vitro sugieren que existe un efecto sinergista cuando se combina quinupristin/dalfopristin con otros agentes antimicrobianos contra algunas cepas de VRE.

CONCLUSIONES: Una bacteremia persistente causada por VRE en un paciente neutropénico fue tratada exitosamente con ampicilina en dosis altas junto con quinupristin/dalfopristin. Datos in vitro y reportes de casos sugieren que esta combinación puede ser una alternativa de tratamiento efectiva para infecciones por VRE que no responden a tratamiento estándar.

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